Reformulation and Drop Size of Apraclonidine Hydrochloride

Mark J. Vocci, M.D., Alan L. Robin, M.D., John C. Wahl, M.D., Phil Mayer, Ph.D., Adrienne Graves, Ph.D., Billie York, Ph.D., Cheryl Enger, M.S., and James Sutton, C.O.T.

We performed a prospective, double-masked, placebo-controlled, six-period, cross-over study in which normal subjects were randomly assigned to treatment and compared three different formulations of apraclonidine hydrochloride (the present commercially available formulation, and formulations with hydroxypropylmethylcellulose or lysolecithin). We also evaluated the efficacy of a 16-µl and 30-µl drop size. The magnitude and duration of decrease in intraocular pressure was comparable for all formulations. Most subjects tolerated all formulations well with only a few reporting any side effects. The best-tolerated formulation was 0.5% apraclonidine hydrochloride delivered with a 16-µl drop size. Dry mouth developed frequently with the commercially available 1% apraclonidine solution. Blurred vision complicated the use of the formulation containing hydroxypropylmethylcellulose. Both dry mouth ($P < .05$) and blurred vision ($P = .004$) were statistically significant side effects.

APRACLONIDINE HYDROCHLORIDE is a relatively selective alpha$_2$-adrenergic agonist and a clonidine derivative. Topical 1.0% apraclonidine is the only medication that consistently reduces intraocular pressure increases accompanying argon laser trabeculoplasty and iridotomy.[1-4] Various concentrations of apraclonidine have reduced intraocular pressure in normal and glaucomatous eyes.[5-8] Dose-related[7] side effects, such as dry mouth, might limit its long-term usefulness. It would be ideal to minimize such symptoms while not altering apraclonidine's ability to reduce intraocular pressure.

These symptoms could possibly be reduced by reformulation and reduction in drop size. Reformulation may allow greater adherence of the medication to the cornea, better corneal penetration, and less systemic absorption. This may allow for a comparable magnitude and duration of intraocular pressure reduction seen with the 1% solution, but with fewer side effects. A similar effect (a reduction in concentration from 0.5% to 0.25% with a comparable intraocular pressure reduction) has been seen with the reformulation of betaxolol hydrochloride.[9]

Previous studies with topical alpha-agonists[10] and beta-blockers[11] suggest that reducing the drop size affects intraocular pressure reduction minimally. The eyelid fornix normally holds less than 20 µl of solution.[12] A smaller eyedrop decreases the amount of medication reaching the eye and may allow for decreased eyelid pumping of the eyedrop and decreased systemic absorption. A smaller eyedrop may deliver a bigger effective dose because washout of medication through tearing would be minimal.

We evaluated the intraocular pressure reduction activity and systemic side effects of various eyedrop sizes, concentrations, and formulations of apraclonidine.

Subjects and Methods

We recruited 29 healthy volunteers who were 21 years of age or older. Subject mean age was 33 ± 10.1 years (range, 21 to 55 years). Five were men, 24 were women, 15 were black, and 14 were white. Subjects were excluded if they had any of the following: recent history of ocular trauma, infection, or inflammatory dis-

Accepted for publication Oct. 25, 1991.

From the Sinai Hospital (Drs. Vocci, Robin, and Wahl and Mr. Sutton) and Wilmer Institute of Johns Hopkins School of Medicine, Baltimore, Maryland (Dr. Robin and Ms. Enger); and Alcon Laboratories, Fort Worth, Texas (Drs. Mayer, Graves, and York).

Reprint requests to Alan L. Robin, M.D., 6115 Falls Rd., 3rd Floor, Baltimore, MD 21209-2226.

ease; any abnormality preventing reliable tonometry; previous intraocular or laser operations; contact-lens wear during the study; monocular vision; unstable cardiopulmonary disease; chronic renal failure; received systemic alpha-agonists within 30 days before the study; or had a history of hypersensitivity to apraclonidine or clonidine. We also excluded women who were pregnant, nursing, or of childbearing potential. The hospital's investigational review board approved the study, and written informed consent was obtained from each subject.

We performed a double-masked, six-period crossover study in which subjects were randomly assigned to treatment using three controls, each with a 30-μl drop size (Table 1). The first was the vehicle of the commercially available 1% solution (placebo). The second was 1% apraclonidine solution. The third was a 30-μl solution of 0.5% apraclonidine with conventional formulation. We compared these to the three following different formulations of apraclonidine using a 16-μl drop size: a 0.5% solution of apraclonidine with hydroxypropylmethylcellulose added; a 0.5% solution of apraclonidine with both hydroxypropylmethylcellulose and the corneal penetration enhancer, lysolecithin, added; and a 16-μl 0.5% ophthalmic solution formulated identically to the commercially available 1% solution. Each subject randomly received all six medications with a one-week washout between periods.

On the first day of each crossover period we measured visual acuity, resting blood pressure, and heart rate, and performed slit-lamp biomicroscopy. We carefully placed only a single drop of study medication in both eyes of each subject. We examined the subjects one, three, eight, and 12 hours later. No topical anesthetic was given or intraocular pressure was measured before instillation of the study medication. This allowed us to evaluate better the efficacy of the corneal penetration enhancer, lysolecithin. Applanation tonometry can abrade the cornea, enhancing the penetration of a topical medication. Applanation tonometry before the administration of a glaucoma medication also does not mimic its use in a clinical situation. By instilling medication in subjects before applanation tonometry, there was no confusion between the effects of the penetration enhancer that we evaluated and the effects of topical anesthetic (proparacaine HCl) or its preservative (benzalkonium chloride) on the cornea.[13]

TABLE 1
DIFFERENCES IN FORMULATION AND DROP SIZE OF APRACLONIDINE MEDICATIONS FOR THE SIX STUDY ARMS

CONCENTRATION OF APRACLONIDINE	DROP SIZE (μL)	FORMULATION
None	30	Conventional
0.5%	30	Conventional
1%	30	Conventional
0.5%	16	Conventional
0.5%	16	Hydroxypropylmethylcellulose
0.5%	16	Hydroxypropylmethylcellulose with lysolecithin

At each subsequent interval, intraocular pressure was measured with Goldmann applanation tonometry. We also measured resting blood pressure and heart rate. Subjects estimated side effects and symptoms on an arbitrary scale from 0 to 9. Mild side effects were rated 1 to 3, moderate side effects were rated 4 to 6, and severe side effects were rated 7 to 9. These symptoms were subjective and we did not attempt to measure their severity objectively. The following symptoms were actively elicited: ocular burning, ocular stinging, ocular itching, ocular dryness, excessive tearing, blurred vision, dry mouth, bad taste in mouth, unusually dry nose, systemic tiredness, and systemic drowsiness.

After the 12-hour examination, we instilled a second drop of study medication in both eyes. Each subject was then given the bottles of study medication and asked to instill one drop in each eye twice daily over the next six days. Each subject was seen again one week later, 12 hours after the last eyedrop instillation. We again carefully instilled only one drop of the same study medication into both eyes of each individual. Subjects were examined at one, three, eight, and 12 hours later as on the first day. The identical sequence of examinations was repeated for the next study phase, after the washout.

We averaged the intraocular pressure readings from both eyes of each volunteer, treating each subject as a unit. Results were reported as mean ± 1 standard deviation. The Bonferroni paired *t*-test was used to evaluate data.

Results

Only one subject did not complete all study visits. This subject completed five of the six

study phases and was eliminated during the final day of the last study phase because of an adverse reaction. No change in the visual acuity of any subject was found at any time during the study.

Baseline intraocular pressure was not measured on any study date. We used the placebo-treatment phase as a baseline value. This represented a normal diurnal curve for each subject. At each interval, we compared the results obtained for each study medication with those obtained during placebo treatment at the same interval (Table 2, Figure). All formulations of apraclonidine significantly reduced intraocular pressure, compared to placebo ($P < .05$). The maximal intraocular pressure reduction effect from placebo for all agents was observed at three hours (21.9% ± 16.6% to 26.0% ± 15.6%) and decreased to the range of 10% ± 19.6% to 16% ± 18.2% by 12 hours. Statistical analysis comparing each formulation to all other formulations showed no significant differences for any formulation. A similar intraocular pressure reduction was seen on Day 7 for all formulations. Comparison of intraocular pressure reduction efficacy of all formulations on Day 1 compared with Day 7 yielded no significant differences at all intervals.

The number of subjects whose intraocular pressure was reduced 20% by the placebo for all formulations was determined (Table 3). The 30-μl drop 0.5% apraclonidine solution with conventional formulation reduced intraocular pressure significantly more than the formulation containing both hydroxypropylmethylcellulose and lysolecithin on Day 7 at three hours. Although no other significant difference was observed, the 30-μl drop 0.5% apraclonidine with conventional formulation appeared to reduce intraocular pressure better than all other medications at this interval. No difference was found for any other formulations at any time point.

The percent change of mean systolic blood pressure ranged from −5.2% ± 10.4% to +5.0% ± 15.0% and the percent change of mean diastolic blood pressure ranged from −8.5% ± 12.3% to +5.8% ± 18.1%. No statistically significant differences ($P < .05$) were observed in the percent change from baseline value for systolic and diastolic blood pressure for any agent.

Data for the following side effects were not statistically different (nor did they approach significance) from placebo: burning, stinging, itching, tearing, dry nose, and bad taste. Data for side effects that were significantly different than those of the placebo were also determined (Tables 4 through 7). The formulation containing hydroxypropylmethylcellulose induced significantly more blurred vision than all other formulations ($P = .004$). The placebo induced significantly less ($P < .05$) dry mouth than apraclonidine 1% ($P = .002$), 16-μl 0.5% apraclonidine with conventional formulation ($P = .032$), and 30-μl 0.5% apraclonidine with conventional formulation ($P = .032$) but neither formulation with hydroxypropylmethylcellulose. Apraclonidine 1% induced significantly ($P = .022$) more dry mouth than both formulations with hydroxypropylmethylcellulose. Fatigue and drowsiness were more significant ($P = .016$) with apraclonidine 1% than with placebo. Tiredness was also less frequent ($P = .04$) with placebo when compared with the solution containing hydroxypropylmethylcel-

TABLE 2
MEAN INTRAOCULAR PRESSURE VALUES (± ONE STANDARD DEVIATION)

TIME	APRACLONIDINE WITH CONVENTIONAL FORMULATION			HYDROXYPROPYL-METHYLCELLULOSE	HYDROXYPROPYL-METHYLCELLULOSE WITH LYSOLECITHIN	PLACEBO
	30-μL 1.0%	16-μL 0.5%	30-μL 0.5%			
Day 1						
Hour 1	11.6 ± 2.6	12.4 ± 2.2	12.5 ± 2.8	12.9 ± 3.1	12.4 ± 2.7	14.7 ± 2.5
Hour 3	10.5 ± 2.5	10.9 ± 2.0	10.9 ± 2.4	10.9 ± 2.0	10.5 ± 2.1	14.3 ± 2.3
Hour 8	10.6 ± 2.8	11.7 ± 2.1	11.0 ± 1.9	11.2 ± 2.3	10.8 ± 2.1	13.3 ± 2.2
Hour 12	11.1 ± 2.2	11.7 ± 2.5	11.3 ± 2.6	11.9 ± 2.2	11.4 ± 2.4	13.5 ± 2.6
Day 7						
Hour 1	11.2 ± 2.4	12.5 ± 3.1	11.4 ± 2.8	11.6 ± 2.3	11.9 ± 2.9	14.4 ± 2.3
Hour 3	9.9 ± 2.1	11.1 ± 2.7	10.2 ± 2.5	10.7 ± 1.8	10.9 ± 2.5	13.7 ± 3.0
Hour 8	10.7 ± 2.7	11.8 ± 2.1	11.5 ± 2.2	11.7 ± 2.2	11.4 ± 2.8	13.3 ± 2.8
Hour 12	11.3 ± 2.5	12.0 ± 1.9	12.2 ± 2.3	11.8 ± 2.0	11.9 ± 2.3	13.7 ± 2.3

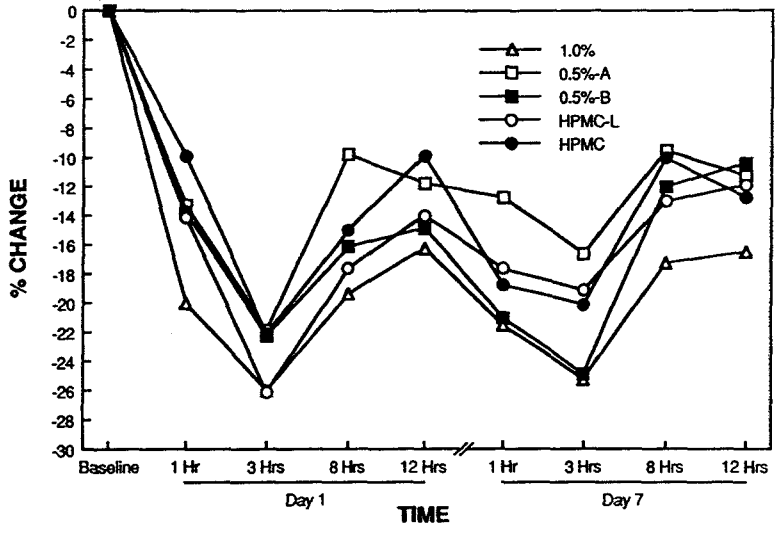

Figure (Vocci and associates). Line graph comparing the percent change in mean intraocular pressure from the placebo-treatment phase for all formulations and drop sizes. The open triangles represent the 30-μl eyedrop of the standard formulation of 1% apraclonidine. The solid squares represent 30-μl eyedrops of 0.5% apraclonidine with the standard formulation. The open squares represent standard formulation of 0.5% apraclonidine with a smaller 16-μl eyedrop size. Both the solid and open circles represent formulations of 0.5% apraclonidine using the smaller 16-μl eyedrop size. The solid circles represent formulations to which hydroxypropylmethylcellulose was added. The open circles represent the formulation to which lysolecithin was also added. No significant difference at any interval was observed between groups. No significant difference was observed in any group between mean percent intraocular pressure change from placebo at comparable times on Days 1 and 7. HPMC-L indicates hydroxypropylmethylcellulose and lysolecithin. HPMC indicates hydroxypropylmethylcellulose.

lulose and lysolecithin. Although the differences in drowsiness and tiredness between the 16-μl 0.5% apraclonidine with conventional formulation and apraclonidine 1% were not statistically significant at the $P \leq .05$ level, eight of the 29 subjects (27%) reported moderate to severe reactions with 1% apraclonidine compared to three of the subjects (10.5%) reporting the same level with the 16-μl 0.5% apraclonidine with conventional formulation. This trend might be significant if a larger sample size is used.

The one subject who was discontinued from the study reported the most severe side effect at Day 7 of her final study visit while receiving apraclonidine 1%. Before instillation of the medication on the last day of the study, this subject reported mildly blurred vision, burning, and photophobia. Slit-lamp biomicroscopy disclosed bilateral mild corneal punctate staining, mild conjunctival injection, and trace cell and flare in the anterior chamber. Two additional subjects receiving apraclonidine 1% had sparse corneal punctate staining but were asymptomatic. A mild headache was reported by two subjects receiving the 30-μl 0.5% apraclonidine with conventional formulation on Day 1. Nine subjects reported subjective mild blurring of vision after the instillation of both solutions containing hydroxypropylmethylcellulose. Five of these nine subjects reported that the blurring was transient, lasting less than one minute. Headache was reported by two subjects while using the formulation containing hydroxypropylmethylcellulose with lysolecithin.

Discussion

This study used a potentially commercially available eyedrop bottle that delivers a 16-μl drop size. Previous studies of other medications that used minidrops used either pipettes[10] or a prototype drop bottle.[11] We also evaluated multiple formulations and concentrations. Baseline intraocular pressure was not measured and the intraocular pressure data were analyzed as percent change from placebo. The data obtained from the placebo-treated group separated the pharmacologic effects of apraclonidine from diurnal variation and placebo effects.

TABLE 3
NUMBER OF SUBJECTS WITH A 20% REDUCTION IN INTRAOCULAR PRESSURE

TIME	APRACLONIDINE WITH CONVENTIONAL FORMULATION			HYDROXYPROPYL-METHYLCELLULOSE WITH LYSOLECITHIN	HYDROXYPROPYL-METHYLCELLULOSE
	30-μL 1.0%	16-μL 0.5%	30-μL 0.5%		
Day 1					
Hour 1	16	11	12	13	12
Hour 3	20	19	19	21	19
Hour 8	16	11	14	12	13
Hour 12	14	10	12	15	10
Day 7					
Hour 1	18	14	17	12	15
Hour 3	14	15	22*	13*	14
Hour 8	13	9	9	10	10
Hour 12	13	7	10	10	11

*30-μl 0.5% apraclonidine with conventional formulation significantly reduced intraocular pressure in more volunteers by 20% compared to hydroxypropylmethylcellulose with lysolecithin.

This method was important because statistically significant decreases in intraocular pressure have been observed in eyes in which placebo drops have been instilled.[7,14-16]

The data regarding the effect of the corneal penetration enhancer, lysolecithin, would have been confounded by the previous applanation of an anesthetized cornea had a baseline intraocular pressure been obtained. However, the main disadvantage of this study was that the data were calculated as a percent change from placebo rather than from baseline value. This may under- or overestimate the intraocular pressure-reducing ability of various formulations.

This study was conducted to determine whether reformulation or reduction in drop size, or both, of topically administered apraclonidine would affect its ocular hypotensive effects and its side effect profile. All formulations significantly reduced intraocular pressure compared to placebo. No significant differences in the average maximal intraocular pressure reduction were found for any formulation at any time point in the study compared to any other formulation. The maximal intraocular pressure-reducing effect was observed at three hours for all formulations. This was consistent with findings of previous studies.[6,7,17] The range of maximal response in this study varied from 21.9% ± 16.6% to 26.1% ± 15.6%. This range of maximal response was similar to previous apraclonidine studies,[7,17] which reported a 22.4% and 28.6% maximal response with 1% and 0.5% apraclonidine, respectively. Although our study used healthy adult volun-

TABLE 4
NUMBER OF SUBJECTS EXPERIENCING BLURRED VISION AS A SIDE EFFECT (N = 29)

	RATING OF SIDE EFFECT		
	NONE OR MILD	MODERATE	SEVERE
Placebo	29	0	0
Apraclonidine 1%	29	0	0
16-μl 0.5% apraclonidine with conventional formulation	29	0	0
30-μl 0.5% apraclonidine with conventional formulation	29	0	0
Hydroxypropylmethylcellulose with lysolecithin	24	5	0
Hydroxypropylmethylcellulose	20	6	3

TABLE 5
NUMBER OF SUBJECTS EXPERIENCING DRY MOUTH AS A SIDE EFFECT (N = 29)

	RATING OF SIDE EFFECT		
	NONE OR MILD	MODERATE	SEVERE
Placebo	29	0	0
Apraclonidine 1%	16	9	4
16-μl 0.5% apraclonidine with conventional formulation	23	4	2
30-μl 0.5% apraclonidine with conventional formulation	23	6	0
Hydroxypropylmethylcellulose with lysolecithin	25	2	2
Hydroxypropylmethylcellulose	25	3	1

TABLE 6
NUMBER OF SUBJECTS EXPERIENCING DROWSINESS AS A SIDE EFFECT (N = 29)

	RATING OF SIDE EFFECT		
	NONE OR MILD	MODERATE	SEVERE
Placebo	29	0	0
Apraclonidine 1%	23	2	4
16-μl 0.5% apraclonidine with conventional formulation	28	1	0
30-μl 0.5% apraclonidine with conventional formulation	27	1	1
Hydroxypropylmethylcellulose with lysolecithin	26	3	0
Hydroxypropylmethylcellulose	27	1	1

TABLE 7
NUMBER OF SUBJECTS EXPERIENCING TIREDNESS AS A SIDE EFFECT (N = 29)

	RATING OF SIDE EFFECT		
	NONE OR MILD	MODERATE	SEVERE
Placebo	28	1	0
Apraclonidine 1%	21	2	6
16-μl 0.5% apraclonidine with conventional formulation	26	2	1
30-μl 0.5% apraclonidine with conventional formulation	26	2	1
Hydroxypropylmethylcellulose with lysolecithin	21	7	1
Hydroxypropylmethylcellulose	25	3	1

teers, these results probably corresponded to potential short-term results seen in glaucomatous eyes as the results of our study were similar to those seen when topical apraclonidine was instilled in both healthy and glaucomatous eyes.[6]

The effective dose of all formulations of 0.5% apraclonidine with a reduced (16-μl) drop size is approximately one drop of a 0.25% solution. A previous dose-response study[7] that used concentrations of 0.125%, 0.25%, and 0.5% apraclonidine in subjects with ocular hypertension and glaucoma found no statistically significant differences between 0.25% and 0.5% solutions. The previous dose-response study[7] did find a difference in the percentage of patients with a greater than 20% reduction in intraocular pressure at eight hours for the 0.25% and 0.50% solutions. However, as in our present study, this difference did not attain significance with the exception of the formulation with hydroxypropylmethylcellulose and the conventional 30-μl 0.5% apraclonidine solution. Hydroxypropylmethylcellulose might lessen the effective concentration of apraclonidine.

The magnitude and duration of responses was similar for Day 1 and Day 7. The range of magnitude and duration of response was similar to that in previous studies using similar concentrations of apraclonidine.[7,17] This may indicate that short-term studies of apraclonidine could be as brief as 24 hours.

We detected no clinically or statistically significant differences in resting systolic or diastolic blood pressure or pulse rate in this study. Similar findings have been reported in several studies.[5,6,18]

The most commonly elicited side effects in our study were dry mouth, dry nose, fatigue, drowsiness, and burning on instillation. Fewer subjects reported side effects while taking 16-μl 0.5% apraclonidine with conventional formulation, the 30-μl 0.5% apraclonidine with conventional formulation, and both formulations containing hydroxypropylmethylcellulose when compared to apraclonidine 1% for fatigue, dry mouth, and bad taste. However, the decrease in side effects was not entirely dose-dependent. The trend was as might be expected; lower doses of apraclonidine were associated with a decrease in the number of subjects reporting complications, and the complications that were reported were milder. The only exception was transient blurring of vision induced by the formulations containing hydroxypropylmethylcellulose. This was subjective and visual acuity was not measured after the instillation of apraclonidine. This was most likely caused by the increased viscosity of hydroxypropylmethylcellulose. The addition of hydroxypropylmethylcellulose offered no apparent advantages, but had the disadvantage of blurred vision.

All subjects spontaneously volunteered information about the new (16-μl) eyedrop bottle. They agreed it was easier to squeeze and deliver one drop with this bottle and therefore preferred the new eyedrop bottle to the conventional eyedrop bottle.

Although the side effects were tolerable for the subject group as a whole, some of these side effects may limit the future applications of the drug in susceptible individuals. One subject developed mild ocular irritation and anterior

chamber inflammation representative of an allergic reaction during the one-week instillation period with the apraclonidine 1% formulation. This reaction developed during the subject's sixth study phase and did not develop with any other formulation or drop size. This unusual reaction has been previously reported with 1% apraclonidine[17] and may represent a problem when used for long-term treatment of glaucoma. It is noteworthy that this reaction developed during the final phase (Week 6) of the study and may be related to the total duration of apraclonidine exposure.

This study demonstrated that reformulation or reduction in drop size, or both, is associated with a similar duration and magnitude of intraocular pressure reduction but can also be associated with a decrease in local and systemic side effects. Decreased eyelid pumping of a smaller drop volume contributed to the effects found in this study. These short-term results augur well for the future long-term instillation of apraclonidine hydrochloride as an ocular hypotensive agent in the management of glaucoma. Apraclonidine, when used in long-term treatment, may be most effective in a smaller drop size. A new long-term agent for the treatment of glaucoma must not only be safe and effective, but also have tolerable side effects. Apraclonidine in the form of the 0.5% solution with a 16-μl drop size was both effective and well-tolerated.

References

1. Robin, A. L., Pollack, I. P., House, B., and Enger, C.: Effects of ALO 2145 on intraocular pressure following argon laser trabeculoplasty. Arch. Ophthalmol. 105:646, 1987.

2. Robin, A. L., Pollack, I. P., and deFaller, J. M.: Effects of topical ALO 2145 (p-aminoclonidine hydrochloride) on the acute intraocular pressure rise following argon laser iridotomy. Arch. Ophthalmol. 105:1208, 1987.

3. Brown, R. H., Stewart, R. H., Lynch, M. G., Crandell, A. S., Mandell, A. I., Wilensky, W. T., Schwartz, A. L., Gaasterland, D. E., deFaller, J. M., and Higginbotham, E. J.: ALO 2145 reduces the intraocular pressure elevation after anterior segment laser surgery. Ophthalmology 95:378, 1988.

4. Robin, A. L.: The role of apraclonidine hydrochloride in laser therapy for glaucoma. Trans. Am. Ophthalmol. Soc. 87:729, 1989.

5. Abrams, D. A., Robin, A. L., Pollack, I. P., deFaller, J. M., and DeSantis, L.: The safety and efficacy of topical 1% ALO 2145 (p-aminoclonidine hydrochloride) in normal patients. Arch. Ophthalmol. 105:1205, 1987.

6. Abrams, D. A., Robin, A. L., Crandall, A. S., Caldwell, D. R., Schnitzer, D. B., Pollack, I. P., Rader, J. E., and Reaves, T. A.: A limited comparison of apraclonidine's dose response in subjects with normal or increased intraocular pressure. Am. J. Ophthalmol. 106:230, 1989.

7. Jampel, H. D., Robin, A. L., Quigley, H. A., and Pollack, I. P.: Apraclonidine. A one week dose response study. Arch. Ophthalmol. 106:1069, 1988.

8. Morrison, J. C., and Robin, A. L.: Adjunctive glaucoma therapies. A comparison of apraclonidine and dipivefrin when added to timolol maleate. Ophthalmology 96:3, 1989.

9. Weinreb, R. N., Caldwell, D. R., Goode, S. M., Horwitz, B. L., Laibovitz, R., Shrader, C. E., Stewart, R. H., and Williams, A. T.: A double-masked three month comparison between 0.25% betaxolol suspension and 0.5% betaxolol ophthalmic solution. Am. J. Ophthalmol. 110:189, 1990.

10. Petursson, G., Cole, R., and Hanna, C.: Treatment of glaucoma using minidrops of clonidine. Arch. Ophthalmol. 102:1180, 1984.

11. Brown, R. H., and Lynch, M. G.: Design of eyedropper tips for topical beta-blocking agents. Am. J. Ophthalmol. 102:123, 1986.

12. Holly, F. J., and Lemp, M. A.: Wettability and wetting of corneal epithelium. Exp. Eye Res. 11:239, 1971.

13. Camber, O., and Edman, P.: Influence of some preservatives on the corneal permeability of pilocarpine and dexamethasone. Int. J. Pharmacol. 39:229, 1984.

14. Caldwell, J. R., Salisbury, G. R., and Guzek, J. P.: Effect of topical betaxolol on ocular hypertensive patients. Arch. Ophthalmol. 102:539, 1984.

15. Partamian, L. G., Kass, M. A., and Gordon, M.: A dose response study on the effect of levobunolol on ocular hypertension. Am. J. Ophthalmol. 95:229, 1983.

16. Zimmerman, T. J., and Kaufman, H. E.: Timolol. Dose response and duration of action. Arch. Ophthalmol. 95:605, 1979.

17. Robin, A. L.: Short-term effects of 1% apraclonidine therapy. Arch. Ophthalmol. 106:912, 1988.

18. Hernandez, Y., Hernandez, H., Cervantes, R., Frati, A., Hurtado, R., McDonald, T. O., and DeSousa, B.: Cardiovascular effects of topical glaucoma therapies in normal subjects. J. Toxic Cut. Ocular Toxicol. 2:99, 1983.